

REVIEW ARTICLE

The Effect of Early Fluid Resuscitation on Mortality in Sepsis: A Systematic Review and Meta-Analysis

OBJECTIVES: While general agreement exists on many sepsis management principles, the details of early fluid resuscitation in sepsis remain contentious. The aim of the current review is to examine the impact of early (≤ 8 hr) fluid dosing, timing, and guideline-based resuscitation on mortality in sepsis.

DATA SOURCES: PubMed, Scopus, Cochrane, and Google Scholar from January 1, 2000, to November 8, 2024.

STUDY SELECTION: Randomized controlled trials and observational data, adjusting for confounding, for adults (≥ 18 yr) with sepsis.

DATA EXTRACTION: From 2,169 citations, 30 studies with 119,583 patients were included.

DATA SYNTHESIS: Dosing: three randomized trials suggest no mortality difference between more liberal (~ 43 – 72 mL/kg) vs. more restrictive (as low as 30 mL/kg) fluid resuscitative strategies (relative risk, 1.00 [0.81 – 1.24]). Eleven of 13 studies observed mortality risk when low-fluid volumes were administered (< 20 mL/kg; effect direction/sign test: $p < 0.001$). Six of 11 studies observed mortality risk when fluid volume dosing exceeded higher limits (> 45 mL/kg; $p = 0.55$). Timing: four of four studies observed a survival benefit with earlier completion of 30 mL/kg (within 3 hr; $p = 0.12$). Thirty mL/kg by discrete time: less than or equal to 1 and less than or equal to 2 hours—two studies observed survival benefit; less than or equal to 3 hours—one study observed survival benefit and three studies observed no mortality impact; and less than or equal to 6 hours—two studies observed a survival benefit, four studies observed no impact, and two studies observed increased mortality risk (both > 30 groups received > 50 and > 70 mL/kg).

CONCLUSIONS: For fluid resuscitation within 8 hours of sepsis diagnosis: 1) randomized trials suggest no mortality difference between more restrictive and more liberal fluid resuscitative strategies (certainty of evidence: low); 2) dosing less than 20 mL/kg has an effect on increased mortality (low certainty); 3) observational studies trend toward increased mortality with higher volume resuscitation (> 45 mL/kg) but are not supported by randomized trials (very low certainty); and 4) survival benefit is observed when 30 mL/kg is completed within 3 hours (low certainty).

KEYWORDS: dosing; early; fluids; resuscitation; sepsis; shock

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Sepsis continues to be a leading cause of morbidity and mortality worldwide (1). While rapid detection and treatment are known to be paramount, sepsis definitions and strategies for management remain contentious. In 2001, a landmark trial by Rivers et al (2) showed a dramatic mortality impact with use of a novel resuscitation protocol coined early goal-directed therapy

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KEY POINTS

Question: What is the impact of early (≤ 8 hr from diagnosis) fluid resuscitation on mortality for septic patients based on studies examining fluid dosing, timing, and guideline-based resuscitation goals?

Findings: 1) Randomized trials show no mortality difference between more restrictive and more liberal fluid resuscitative strategies; 2) dosing less than 20 mL/kg has an effect on increased mortality; 3) observational studies trend toward increased mortality with larger volume resuscitation (> 45 mL/kg) but are not supported by randomized trials; and 4) survival benefit is observed when 30 mL/kg is completed within 3 hours.

Meaning: While tailored fluid resuscitation based on the individual patient remains the goal, until a more formalized strategy becomes available, early-stage, fluid dosing guidance remains prudent. Our findings support a U-shaped relationship between fluid volumes and mortality, making the current Surviving Sepsis Campaign fluid dosing guidance of 30 mL/kg within 3 hours of sepsis-induced hypoperfusion a reasonable recommendation. Future trials to further distinguish resuscitation targets based on an individual's bedside assessment and comorbid status are needed.

that provided an early framework for the Surviving Sepsis Campaign (SSC) (3). Over time, some of the tenets of early goal-directed therapy came into question and eventually had fallen out of favor after three major trials showed no benefit over usual care (4–6). Specific to fluid resuscitation, the SSC had adapted their recommendations based on the average fluid volumes administered within these trials and “strongly” recommended the administration of 30 mL/kg of crystalloids within 3 hours of sepsis-induced hypoperfusion. It was stated that this fixed volume was meant to “allow clinicians to initiate resuscitation while obtaining more specific information...and...more precise measurements of hemodynamic status,” although this recommendation was noted to be based on low-quality evidence devoid of supporting controlled data (7).

There is evidence that downstream positive fluid balances and higher volume fluid administration measured “days” into hospitalization are associated

with increased mortality (8–12). This led to increasing concern over the potentially aggressive and indiscriminate nature of the 30 mL/kg recommendation that did not provide exceptions for more volume-sensitive conditions (13–17). Therefore, the SSC published new guidelines that “weakly” recommended that 30 mL/kg be administered within 3 hours and no longer specified the initiation of fluids as part of a 1-hour treatment bundle (18). Further, there has been some divergence in a policy statement by the American College of Emergency Physicians (ACEP). ACEP does not support the “prespecified volume of fluid for all patients,” stating that the initial administration of “500–1000 mL of crystalloid is a common and reasonable practice” and should be further guided by patient response but recognize that “many patients benefit from 30 mL/kg of crystalloid” (19).

Thus, there remain competing views regarding the role of fluids in sepsis-based resuscitation. Prespecified fluid minimums may ensure that more patients are receiving vital volume replacement that may otherwise be missed as bedside assessments are not yet reliable or feasible early in current sepsis care. However, given the concern for excessive fluid administration, recent studies are attempting to determine whether more tailored resuscitative strategies, such as inclusion of earlier vasopressors, may be a safer alternative (20, 21). Therefore, we aimed to analyze the impact of early fluid resuscitation on sepsis-based mortality through a meta-analysis and systematic review.

MATERIALS AND METHODS

This systematic review was registered with PROSPERO (CRD42021245431; https://www.crd.york.ac.uk/prospere/display_record.php?RecordID=245431) and was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (S.1, <https://links.lww.com/CCM/H748>) (20). With the assistance of a medical librarian, references from PubMed, Scopus, Cochrane Central Register of Controlled Trials, and the first 300 Google Scholar references (21) were queried between January 1, 2000, and November 8, 2024. This time frame was selected to include studies before and around the advent of early goal-directed therapy (2). S.2 and S.3 (<https://links.lww.com/CCM/H748>) show details of the search strategy.

Inclusion Criteria

The overarching objective was to examine the impact of early fluid resuscitation (within 8 hr of onset) on mortality for adult patients with a minimum of severe sepsis or sepsis, defined by Sepsis-2 or Sepsis-3 guidelines (or similar substitute), respectively. Eight hours from sepsis onset was specifically chosen to best capture early fluid resuscitation, attempting to exclude more downstream phases in resuscitation, and to include seminal trials on this topic. Within this broad context, we had a few secondary objectives: 1) timing of fluid initiation (previously published) (22); 2) speed of completing a fluid bolus—prespecified volumes (typically 20–30 mL/kg) evaluated at guideline-based time periods (i.e., 3 and 6 hr); and 3) a subgroup analysis of objectives 1) and 2), focusing on patient populations vulnerable to fluid overload (e.g., congestive heart failure, renal failure). We specified the possibility of ad hoc studies depending on the results of the literature review. Additional studies were added post hoc examining optimal fluid dosing. Given the breadth of this topic, objective 3) will be completed separate of this review.

Included studies needed to be randomized controlled or observational while providing mortality-based odds ratios (or comparable) adjusting for potential confounders. Adult age was defined as 18 years old or older and fluids were defined as only crystalloid administered.

No animal-based studies or studies primarily evaluating the administration of colloids or blood products were considered. Further, case reports, case series, narrative reviews, and systematic reviews were also excluded. Additionally, studies exclusively evaluating potentially volume-sensitive conditions, including heart failure, end-stage renal disease, liver disease, obesity, patients who develop acute lung injury/acute respiratory distress syndrome, and cohorts from low- to middle-income countries where traditional intensive-level care may not be available were excluded (23, 24). Thus, studies may contain these various volume-sensitive subgroups as part of the general study population. Further detail and other study considerations are detailed in S.4 (<https://links.lww.com/CCM/H748>).

Study duplicates were removed through an automated process with the assistance of the medical librarian. An initial screening of all studies was completed by author (M.A.W.) to remove studies clearly not meeting criteria based on the title and abstract.

Two authors (M.A.W., H.I.K.) independently screened the remaining studies for final inclusion in the review.

Data Collection and Quality

The study variables listed in **Supplementary Tables 1 and 2** (<https://links.lww.com/CCM/H748>) were independently collected by authors (M.A.W., H.I.K.). Bias assessment for each observational study was assessed using the CLARITY tool (25) and for each randomized trial using the revised Cochrane risk-of-bias tool (26). A preestablished criterion for reaching various ratings of bias is further defined in S.5 (<https://links.lww.com/CCM/H748>).

A quality assessment was performed using the Grading of Recommendations Assessment, Development, and Evaluation Working Group, in conjunction with the Cochrane Handbook 6.0 (27, 28).

Statistical Analysis

After collation of included study results, four novel research questions were derived to best inform study objective number 2 (S.6, <https://links.lww.com/CCM/H748>, in Population, Intervention, Comparison, and Outcome [PICO] format): 1) impact of resuscitation protocols using more restrictive vs. more liberal fluid strategies; 2) impact of low-volume dosing (< 20 mL/kg); 3) impact of high-volume dosing (> 45 mL/kg); and 4) impact of timing of fluid administration (< 3 hr).

When studies had similar clinical questions and comparable methods, we executed random effects meta-analysis with the Hartung-Knapp estimator of the CIs. Analyses were conducted using the metabin function of the meta package for the R statistical programming language (R Development Core Team, Auckland, New Zealand) (29). We reported I^2 , corresponding intervals, and qualitative interpretation of the I^2 per Cochrane labels (30). When the data allowed, results were displayed using an arrow plot (31).

Meta-analysis did not appear acceptable for specific outcomes related to fluid timing and low- and high-volume fluid dosing due to heterogeneous study methods and assessment paradigms. Thus, in post hoc fashion, we chose to synthesize these outcomes using sign test with binomial probability based on an effect direction plot as suggested by the Cochrane Handbook.

An additional study grouping assessing 30 mL/kg at discrete time points was formed as this was a common

study design found in the literature. However, insufficient fluid dosing specifics were common; thus, results were used as an adjunct to the other research questions and not more formally synthesized.

Data and statistical code are online and available for sharing at: <https://openmetaanalysis.github.io/sepsis#fluids>.

RESULTS

A total of 2952 citations were identified, including 1659 from PubMed, 513 from Cochrane, 446 from Scopus, 300 from Google Scholar, and 34 discovered through the review of the existing citations as shown in **Supplemental Figure 1** (<https://links.lww.com/CCM/H748>). Supplementary Tables 1 and 2 (<https://links.lww.com/CCM/H748>) show the 30 selected studies that included a total of 119,583 patients with a median mortality = 26.7% (20.0–37.4%).

Fluid Dosing

Eighteen studies analyzed the effect of fluid dosing early in sepsis resuscitation (**Fig. 1**; **Table 1**; and Supplementary Table 2, <https://links.lww.com/CCM/H748>) (4, 32–48). An illustrative approach, described in **S.7** (<https://links.lww.com/CCM/H748>) and presented in Figure 1, groups studies based on the time course for which doses were measured.

More Restrictive Vs. More Liberal Resuscitation Trials. We identified three randomized controlled trials examining the impact of restrictive vs. liberal fluid resuscitation on mortality ($n = 3003$) (4, 32, 33). **Figure 2** contains a forest plot that suggests no mortality impact when more liberal fluids are compared with more restricted fluids resuscitation (relative risk, 1.00; 95% CI, 0.81–1.24). **Supplemental Figure 2** (<https://links.lww.com/CCM/H748>) further summarizes these findings using an arrow plot.

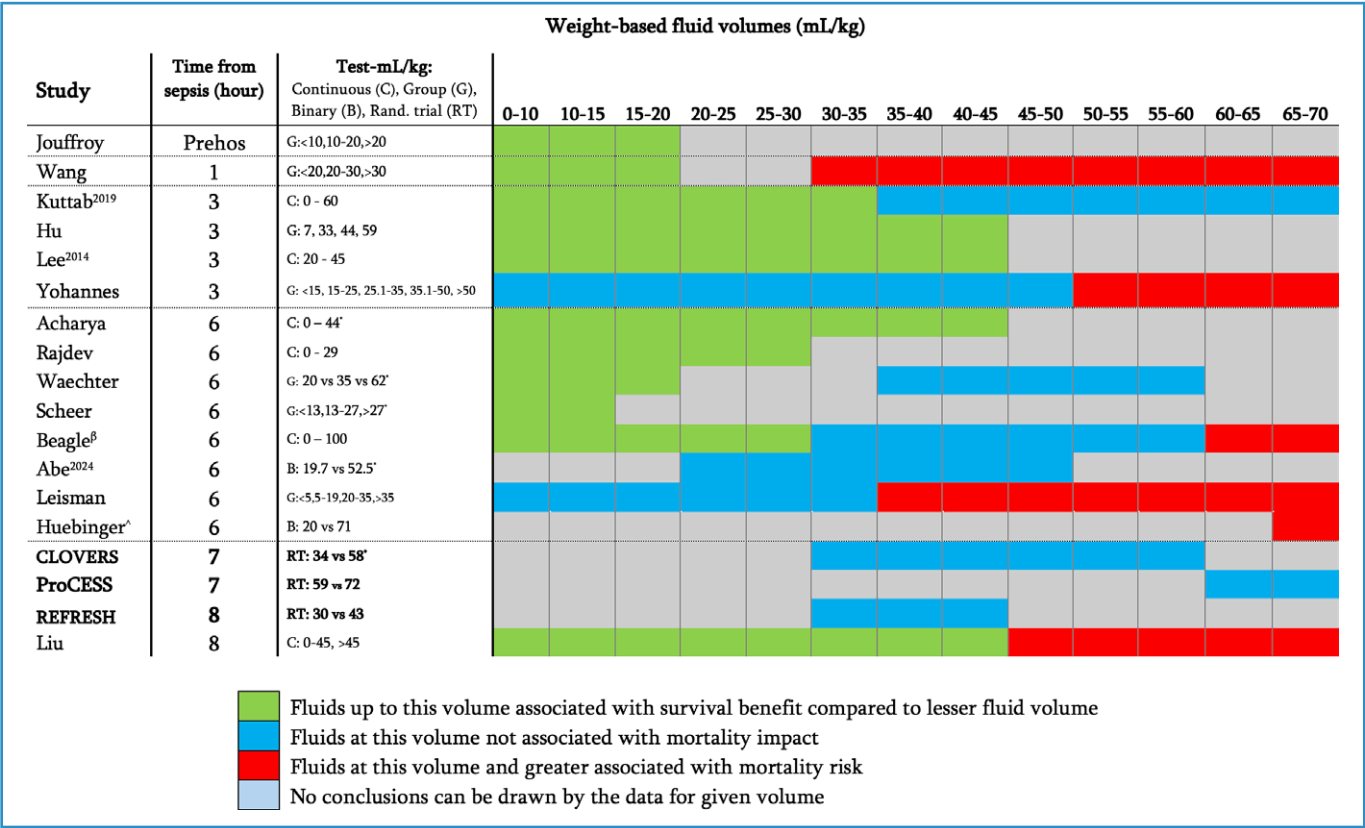


Figure 1. Displays the mortality impact associated per weight-based volume for each listed study, including the time at which this measurement was made with respect to sepsis onset. *Instances where weight-based volumes had to be estimated based on the weights listed within each study or assumed a median weight of 75 kg. The *above color scheme* assumes that fluid resuscitation has a U-shaped relationship with mortality. ⁶Represents *continuous plot* from the cohort without comorbid heart failure requiring intensive care-level based care. B = binary, C = continuous, CLOVERS = Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis trial, Prehos = prehospital, ProCESS = Protocol-Based Care for Early Septic Shock trial, REFRESH = Restricted Fluid Resuscitation in Suspected Sepsis Associated Hypotension trial.

TABLE 1.
Grading of Recommendations Assessment, Development, and Evaluation Quality of Evidence and Summary of Findings

Certainty Assessment		Summary of Findings Based on Mortality			
		No. of Patients or Studies Categorized by Statistical Significance ^a		Effect ^a	Certainty of Evidence
No. of Studies (Design)					Comments
Study question 1: Mortality difference between more liberal and more restrictive fluid strategies					
Three (RCT)	1) Not serious	More liberal Mortality: 200/1274 patients	More restricted Mortality: 199/1286 patients	RR, 1.00 (0.81–1.24)	⊕⊕ Low
	2) Not serious				↓ Differing volume ranges assessed between studies ↓ Few studies included with one low <i>n</i> -size Take away: Evidence suggests No mortality impact
	3) Serious				
	4) Serious				
	5) Undetected				
Study question 2: Mortality impact of receiving low-volume fluid dosing (< 20mL/kg)					
Thirteen (observational)	1) Serious	Low fluid/benefit 0 studies	Low fluids/risk 11 studies	Low fluids/ no impact Two studies	⊕⊕ Low
	2) Not serious			Effect direction/ sign test Low fluids with increased mortality effect; 13/13 studies (<i>p</i> < 0.001)	Observational studies begin low certainty ↓ Sometimes poor confounders control ↑ Dose response (lower fluids = higher mortality) Take away: low fluid dosing may have ↑ mortality effect
	3) Not serious				
	4) Not serious				
	5) Undetected				

(Continued)

TABLE 1. (Continued)
Grading of Recommendations Assessment, Development, and Evaluation Quality of Evidence and Summary of Findings

Certainty Assessment		Summary of Findings Based on Mortality				
1) Risk of Bias 2) Inconsistency 3) Indirectness 4) Imprecision 5) Publication Bias		No. of Patients or Studies Categorized by Statistical Significance ^a		Effect ^a	Certainty of Evidence	Comments
Study question 3: Mortality impact of receiving high-volume fluid dosing (> 45 mL/kg)	Two (RCT), nine (observational)	High fluids/benefit	High fluids/risk	High fluids/no impact	Effect direction/sign test	
	1) Serious	0 studies	Six observational studies	Two RCT, three observational studies	⊕ Very low	Many observational studies begin low certainty
	2) Not serious					↓Poor study control in cases
	3) Not serious					↓Mixed results
	4) Serious					Take away: No mortality effect but evidence very uncertain
Study question 4: Earlier timing (< 3 hr) of fluid administration impact on mortality	5) Undetected					
	Four (observational)	Early fluid/benefit	Early fluid/risk	Early fluid/no impact	Effect direction/sign test	
	1) Serious	Four studies	0 studies	0 studies	⊕⊕ Low	Observational studies begins low certainty
	2) Not serious					↓Poor study control in cases
	3) Not serious					↑Dose response (slower fluids administration = higher mortality)
	4) Not serious					Take away: may have association with ↑mortality; effect limited by low study#
	5) Undetected					

= numbers, RCT = randomized controlled trial, RR = relative risk.

^aIndividual studies were separated by experimental and control groups based on mortality findings or statistical significance, in the case of observational studies. Randomized controlled trial results were meta-analyzed. Study groupings numbers 2–4 required synthesis via effect direction plots and sign tests given differences in patient cohorts and study designs. Effect direction assesses the direction of the finding and does not require statistical difference. Thus, in the case of study grouping number 2, while observations from Yohannes et al (39) (< 15 vs. 25.1–35 mL/kg; odds ratio [OR], 1.026 [0.959–1.098]) did not reach significance, the OR was in the direction of increased mortality. Quality of assessment and summary of findings with respect to the four conclusions derived from this review. The quality assessment was performed using the Grading of Recommendations Assessment, Development, and Evaluation system. Further details are provided within S.7 (<https://links.lww.com/CCM/H748>) outlining the factors used to adjudicate the five domains (limitations, inconsistency, indirectness, imprecision, and publication bias) that may decrease the certainty of evidence.

Forest plot – More liberal versus more restrictive fluids for sepsis with fluid refractory hypotension

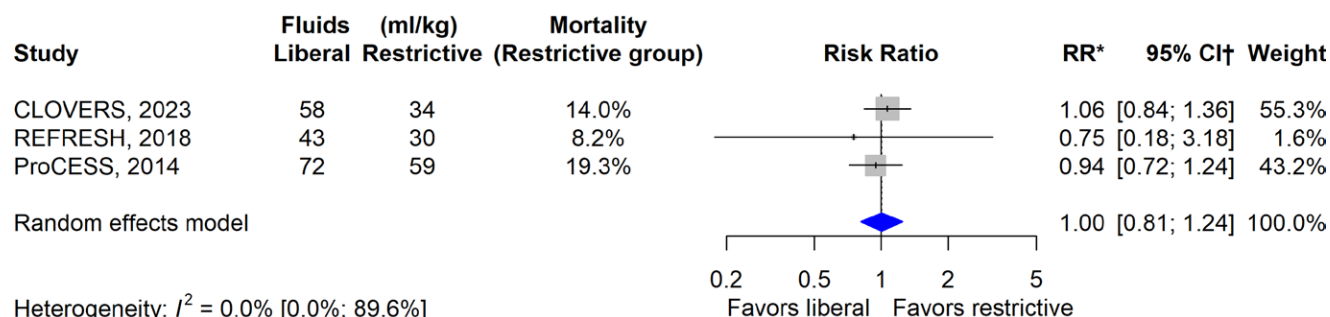


Figure 2. Forest plot showing no mortality impact of more liberal vs. more restrictive fluids resuscitation for sepsis with fluid refractory hypotension for three randomized controlled trials. No mortality difference was found. Protocol-Based Care for Early Septic Shock trial (ProCESS) volumes compared evaluated a “usual care” vs. a “Protocolized Standard Care” group. The early goal-directed therapy (EGDT) group was not included as blood transfusions were part of the protocol and minimal crystalloid volume differences existed between the EGDT and other ProCESS groups. The Protocolised Management in Sepsis (ProMiSe) and Australasian Resuscitation in Sepsis Evaluation (ARISE) trials also had minimal volume differences within their specified groups and were not included in this meta-analysis. CLOVERS = Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis trial; REFRESH = Restricted Fluid Resuscitation in Suspected Sepsis Associated Hypotension trial; RR = risk ratio.

Low-Fluid Dosing (< 20 mL/kg). Thirteen observational studies help to evaluate lower fluid volumes not examined by the included randomized trials with 11 observing increased mortality. An effect direction plot (Supplementary Table 3, <https://links.lww.com/CCM/H748>) shows that low-fluid volumes (< 20 mL/kg) within a prehospital to 8 hours time range had an effect on increased mortality (sign test: $p < 0.001$) (34–44, 46, 48).

High-Fluid Dosing (> 45 mL/kg). Figure 1 illustrates the impact of higher fluid volumes (> 45 mL/kg) on mortality in a 1–8-hour time range. Six of nine observational studies are associated with increased mortality risk, which contrasts with both the Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis Trial (CLOVERS) and Protocol-Based Care for Early Septic Shock trial (ProCESS) trials showing no mortality difference with more liberal fluid resuscitative strategies exceeding 45 mL/kg (4, 32, 35, 36, 39, 42, 44–48). An effect direction plot (Supplementary Table 3, <https://links.lww.com/CCM/H748>) did not show an effect of high fluid dosing on mortality (sign test: $p = 0.55$).

Timing of Fluid Administration

The SSC guidelines include fluid administration time-goal recommendations, which were not evaluated by

the three included randomized trials within this study. Four observational studies were associated with a survival benefit with the early administration of 30 mL/kg (within 1–3 hr) as shown in Figure 3; Table 1; and Supplementary Table 2 (<https://links.lww.com/CCM/H748>) (35, 37, 49, 50). An effect direction plot (Supplementary Table 3, <https://links.lww.com/CCM/H748>) did not reach an effect for fluid administration less than 3 hours (sign test: $p = 0.12$).

Thirty mL/kg at Discrete Time Points (All Studies Observational)

One-, 2-, or 3-Hour Time Points. One study observed a survival benefit when 30 mL/kg was reached within 1 hour of sepsis onset and another when reached within 2 hours (37, 51). At 3 hours, one study observed a survival benefit (36) and three observed no mortality impact (52–54).

Six-Hour Time Point. Two studies observed a survival impact (55, 56), four studies observed no mortality impact (45, 57–59), and one study observed increased mortality when compared with a group not receiving 30 mL/kg with the greater than or equal to 30 mL/kg group estimated to have received 71 mL/kg of crystalloids (47). One study observed no overall impact of receiving 30 mL/kg, however, increased mortality was

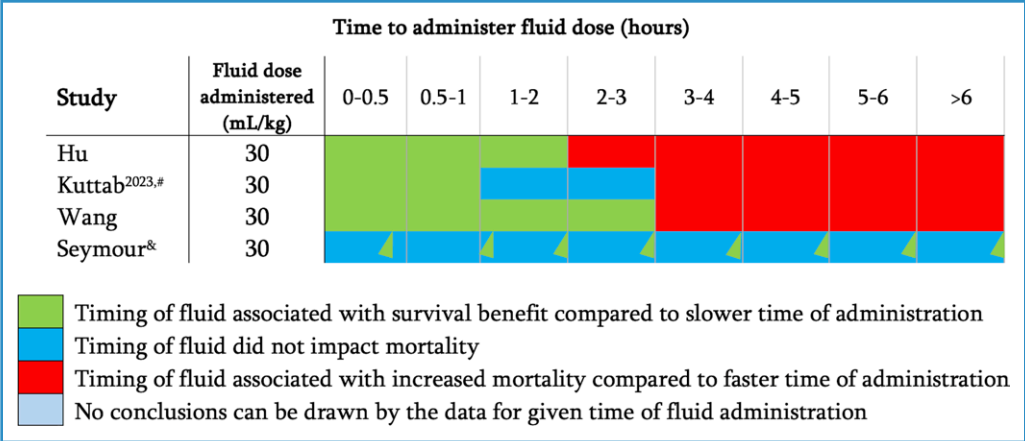


Figure 3. Displays four observational studies analyzing the effect of fluid administration timing on sepsis mortality. Timing is based on estimated sepsis onset with definitions differing between studies. [#]A *continuous plot* observed a linearly increasing mortality risk per hour for reaching 30 mL/kg, although a quadratic term did not reach significance. An additional group analysis only reached significance when receiving 30 mL/kg in less than 1 hr is compared with reaching 30 mL/kg in greater than 24 hr or not at all. less than 1 vs. 1–3, 3–6, and 6–24 hr did not reach significance, although less than 1 vs. 3–6 hr trended toward an impact—odds ratio, 1.83 (0.97–3.52). [&]The original analysis did not observe an impact of fluid timing. When a more inclusive cohort was included (sepsis protocol initiated > 6 hr or 30 mL/kg not reached > 12 hr), a small survival benefit was observed with earlier fluid administration, which has been designated by a *blue rectangle* with a *small green triangle*.

observed for patients with a higher severity of illness (60). All 30 mL/kg-by-timepoint studies are summarized in **Figure 4** and further detailed in Supplementary Table 1 (<https://links.lww.com/CCM/H748>).

Bias Assessment, Quality Grading, and Reconciliation of Reviews

The bias assessment is displayed in **Supplementary Table 4** (<https://links.lww.com/CCM/H748>). Of the 30 included studies, only three were randomized controlled and rated as low risk of bias (4, 32, 33). Most remaining studies were rated “probably yes” with three studies rated “probably no” for low-risk bias based on poor control for sepsis co-interventions and mortality risk.

Supplementary Table 4 and **S.8** (<https://links.lww.com/CCM/H748>) shows the following derivations for the certainty assessment. Question number 1 was downgraded to a low certainty of evidence as studies compared differing median fluid volumes and the ProCESS trial was not specifically designed to assess this question (4). A low-certainty rating was specified for questions numbers 2 and 4—serious issues were raised for risk of bias but upgrades were given in both cases for an observed dose effect. Question number 3

was given a very low certainty rating.

The results and studies included in this systematic review were reconciled with similar reviews (**S.9**, <https://links.lww.com/CCM/H748>) with sparse overlap found (61–65).

DISCUSSION

Overall, the findings of this study support the 30 mL/kg of crystalloid within 3 hours dosing guidelines for sepsis-induced hypoperfusion based on the following observations: 1) randomized trials show no mortality difference between more restrictive and

more liberal fluid resuscitative strategies comparing fluid dosing greater than 30 mL/kg (low certainty) (4, 32, 33); 2) dosing less than 20 mL/kg has an increased risk of mortality effect (low certainty) (34–38, 40–44, 48); 3) observational studies trend toward increased mortality with larger volume resuscitation (> 45 mL/kg) (35, 39, 44, 46–48) but are not supported by randomized trials (very low certainty) (4, 32, 33); and 4) 30 mL/kg within 1–3 hours is associated with survival benefit (low certainty) (35, 37, 49, 50).

Dosing

The three randomized trials meta-analyzed within **Figure 2** suggest no mortality impact when comparing more liberal vs. more restrictive resuscitative strategies based on a low certainty of evidence (4, 32, 33). Specifically, CLOVERS showed no mortality difference between the early vasopressor/restricted fluids group receiving an estimated 34 mL/kg vs. an estimated 58 mL/kg in the liberal fluids group receiving vasopressors an absolute 22% less of the time (32). While this study does not specifically examine the impact of SSC-based dosing of 30 mL/kg, this finding, along with the other randomized trials included, may support the safety of the administration of 30 mL/kg.

Study	Time from sepsis onset (hour)	Overall mortality	<30 vs >30 mL/kg groups	Fluid impact
Jeong ²⁰¹⁹	1	24.7%	Not reported	+
Hu ²⁰²⁰	2	23.9%	Not reported [°]	+
Kuttab ²⁰¹⁹	3	17.1%	12.8 vs 38.3	+
Abe ²⁰¹⁸	3	27.9%	Not reported	+/-
Baghdadi ²⁰²⁰	3	19.0%	Not reported	+/-
Lee ²⁰²¹	3	27.4%	Not reported	+/-
Levy ²⁰¹⁸	6	26.7%	Not reported	+
He ²⁰²³	6	50.4%	Not reported	+
Ferrer ^{^, 2009}	6	41.6%	Not reported	+/-
Miller ^{^, 2013}	6	12.1%	Not reported	+/-
Truong ²⁰¹⁹	6	37.8%	13.3 vs 40 ^{&}	+/-
Abe ²⁰²⁴	6	30.0%	19.7 vs 52.5	+/-
Zheng ^{β, 2023}	6	49.7%	15 vs 45 NR	+/-
Huebinger ²⁰²⁰	6	30.4%	20 vs 71 [*]	-

 Achieving fluid goals associated with survival benefit
 Achieving fluid goals did not impact mortality
 Achieving fluid goal increased mortality

Figure 4. Displays the results from studies that analyze guideline-based dosing from the Surviving Sepsis Campaign where groups are compared based on reaching specific fluid volumes of 30 mL/kg within a specified time period. All studies included were observational. [^]Studies groups separated by less than 20 mL/kg vs. greater than 20 mL/kg. ^βNo mortality impact (marked blue) was found within the entire cohort, which included volumes of 15 vs. 45 mL/kg. However, when the cohort was subanalyzed based on severity of illness (Sequential Organ Failure Assessment ≥ 10), increased mortality (marked red) was found without volumes reported. [°]Three-hr fluid volumes are reported in Hu et al (37) (**Supplement**, <https://links.lww.com/CCM/H748>) but no volumes are reported at 2 hr. [&]This study included previously admitted patients along with emergency department patients and reported volumes did not include preceding volumes 12 hr before the established diagnosis. Thus, volume comparisons would be 40 vs. 53.3 mL/kg including the preceding volume. ^{*}Based on estimated volumes from chart within the Supplement (<https://links.lww.com/CCM/H748>) of 1420 vs. 5310 mL and median weight 74.8 kg taken from the original study. mL/kg = milliliters per kilogram, NR = not reported.

However, the randomized trials do not fully examine other important aspects of fluid dosing and timing. Figure 1 displays the mortality impact of fluid dosing and demonstrates a few notable findings. First, the included observational studies were mostly associated with increased mortality at lower fluid volumes, when 20–30 mL/kg of crystalloids is not reached. Further, Kuttab et al (36) and Beagle et al (44) observe an exponential trendline with steep mortality risk at low-fluid volumes up to ~20–30 mL/kg, which plateau at ~35–45 mL/kg, which supports the presence of

a fluid dose effect. Hu et al (37) observed a similar dose effect; however, the groups receiving lower fluid volume were associated with the later initiation of vasopressors and lower vasoactive-inotropic scores despite a similar severity of illness. Thus, it may be that the patients receiving a more aggressive combination of fluids and vasopressors, altogether, experienced better outcomes. Two studies evaluating 20 mL/kg of fluid combined with the initiation of vasopressors for mean arterial pressure less than 65 observed a survival benefit when completed within 6 hours but were not formally included within this analysis as these treatments were jointly examined (66, 67).

Six observational studies were associated with increased mortality with higher fluid dosing early in the resuscitation of sepsis with 45 mL/kg potentially representing an important threshold

(Fig. 1) (35, 39, 44, 46–48). Liu et al (48) observed a statistical inflection point at 45 mL/kg whereby increasing fluids volumes between 0 and 45 mL/kg were associated with survival benefit but increased mortality risk was observed for volumes exceeding 45 mL/kg. However, the CLOVERS and ProCESS trials do not support this observation as neither show a mortality impact when comparative liberal fluids resuscitative strategies exceed 45 mL/kg (4, 32). Unfortunately, median fluid volumes between groups were not available in either Wang et al (35), Leisman et al (46), Yohannes

et al (39), or Liu et al (48) studies to provide further insight into these observations.

Timing

In a previously reported meta-analysis, we observed a survival benefit with the early “initiation” of fluids in hypotensive patients (22). As part of this review, we selected studies examining the timing of fluid “completion” (20–30 mL/kg) and observed similar results, albeit with some exceptions. For studies evaluating the administration of fluids over a time range, four observational studies were associated with survival benefit with earlier vs. later administration (Fig. 3 and Table 1) (35, 38, 49, 50). When evaluating fluid dosing at discrete time points, results support a survival benefit or observe no mortality impact with early fluid administration when measured between 1 and 3 hours (36, 37, 51–54) but become mixed when measured at 6 hours (45, 47, 55–60).

This 6-hour finding may be partly explained by differences in higher dosing observed within individual studies. Huebinger et al (47) observed increased mortality when volumes exceed 30 mL/kg but compared median volumes of 20 vs. 71 mL/kg. For comparison, the liberal fluids group within the CLOVERS trial received an estimated 58 mL/kg and did not show any mortality difference to a fluid restricted group (32). Further, 20 mL/kg may represent an important threshold where resuscitative volumes less than this are consistently associated with increased mortality risk (Fig. 1). Similarly, Zheng et al (60) observed increased mortality when reaching 30 mL/kg only within a Sequential Organ Failure Assessment greater than 10 subgroup. However, “overall” median volumes were 12 vs. 44 mL/kg but did not specify volumes within this sicker cohort where larger volumes are commonly administered. Further, Zheng et al (60) reports 24-hour volumes in which the “liberal” group received 96 mL/kg of crystalloid, which exceeds amounts typically reported (CLOVERS trial = restricted and liberal groups received ~49 vs. ~74 mL/kg in 24 hr, respectively) (32).

In contrast, He et al (56) observed a survival benefit when reaching 30 mL/kg; however, the less than 30 mL/kg group likely received less than 10 mL/kg (per footnotes of Supplementary Table 1, <https://links.lww.com/CCM/H748>), a range more strongly associated with heightened mortality risk. Taken together, details specific to median dosing are important to consider for studies comparing

groups evaluating target fluid volumes. Notably, less than half of the studies selected had this information available and for the studies in which this was available, some degree of estimation was often required.

Assuming that the early timing of fluid administration are important to sepsis outcomes, it seems likely that a treatment window exists in which the benefits of early fluid resuscitation may diminish over time. Leisman et al (68) observed that reaching a fluid target after 2 hours of sepsis onset is associated with refractory hypotension and increased mortality. There is some concern that more aggressive, early fluid resuscitation may contribute to downstream positive fluid balances; however, the deleterious impacts with more positive fluid balances are observed days into the hospital stay and not during early resuscitation (10–12, 69, 70). Taken together, the recommendation for the administration of fluid within 3 hours of sepsis onset, as part of the SSC guidelines, may be beneficial (18).

Potentially Volume-Sensitive Groups

Current SSC fluid-resuscitation guidelines are indiscriminate of various volume-sensitive conditions, which have fueled concerns over appropriate fluid dosing. In brief, there has been no observable evidence for increased mortality risk (and, in some cases, survival benefit) associated with administration of 30 mL/kg early in the resuscitation for end-stage renal disease (32, 36, 41, 46, 47, 71, 72) and for patients who later develop acute lung injury (73). Similar findings were observed for septic patients with congestive heart failure (32, 40, 46, 71, 72, 74, 75), albeit with more recent evidence suggesting benefit with fluid moderation (44, 76). Last, two Zambian-based trials showed harm with protocolized resuscitation including fluids, dopamine, and blood transfusion. However, these cohorts possessed high prevalence of tuberculosis, HIV/AIDS, malaria, and/or anemia where traditional intensive-level care were not available (23, 24). This topic is outside the scope of this review and is not further explored.

Strengths and Limitations

Strengths include the following: 1) the inclusion of 30 studies allowed for important interpretations based on patterns observed between similar studies and 2) we were unable to find a similar systematic review and are hopeful this study will provide novel insights into this important topic.

Many limitations need to be closely considered when interpreting the results of this review. First, most included studies are observational and subject to issues of endogeneity, whereas it is difficult to disentangle the relationship between fluid volume, disease severity, and mortality. As noted, conclusions are based on low certainty or very low certainty evidence. Next, important group differences, including median fluid volumes, prevalence of hypotension or septic shock, or other markers of disease severity may impact the effect of fluid administration and mortality risk but were not consistently reported. Studies observing the early benefits of fluids often report a differential effect favoring a higher severity of illness (36, 46, 77). Further, early resuscitation is likely effective based on attempts to rapidly correct hypoperfusion states through a combination of efforts, including both fluid administration and vasopressors. The highest quality evidence included within this analysis attempts to determine which strategy may provide the best outcomes with no mortality difference found. Although, important differences exist between these randomized trials, which limit their combined interpretation. Future studies should assess how individual protocols impact resuscitation and outcomes while considering applicability to current clinical practice.

CONCLUSIONS

SSC recommendations for 30 mL/kg by 3 hours may provide reasonable guidance based on this review's findings. We provide conclusions more in the spirit of possible fluid administration guidance vs. strict dosing mandates as optimal resuscitation likely remains best tailored to each individual patient. Until this individualized resuscitative strategy is formalized, dosing and timing guidance remain useful.

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